REMARKS

Consideration of the application as amended above is respectfully requested.

Claims 1-9, 11-17 and 24 were pending in the present application. Claims 3 and 12 have been canceled in the present amendment. Claims 1, 2-9, 11 and 24 have been amended. New Claim 25 has been added. Presently, Claims 1-2, 4-9, 11, 13-17, 24 and 25 are pending in the present application.

Claim 1 has been amended to delete hydrogen and SR^b from the Markush group for R^1, and to specify that R^1 is not $-NH_2$. This deletion of elements from a Markush group does not add new matter to the claims. The Claim has further been amended to incorporate the limitations on R^3 and R^4 provided in original Claim 3, and Claim 3 has been canceled.

Claims 2, 4-9 and 24 have been amended by replacing "and pharmaceutically acceptable salts thereof" with "or a pharmaceutically acceptable salt thereof" to present the claim in proper Markush form. This amendment does not add new matter to the present application.

Claim 4 has been further amended to delete the element "$-SC_{1-6}$alkyl, unsubstituted or substituted with one to three R^c substituents" from the Markush group for R^1.

Claim 5 has been further amended to delete "hydrogen" from the Markush group for R^8 in element (10) of the definition of R^1. This deletion of an element from a Markush group does not add new matter to the present claims.

Claim 8 has been amended to correct the numbering of the Markush groups for R^1 and R^2. Support for this amendment is found at page 6, line 24 to page 7, line 27 and at page 9, line 21, to page 10, line 14. Claim 8 has also been amended to delete amino from element 10 of R^1, and to delete $-SCH_3$ from the Markush group for R^1, and to correct a typographical error by replacing "pyrrolidnyl" in element (10) with "pyrrolidinyl." These amendments do not add new matter to the present application.

Claim 11 has been amended to incorporate the specific conditions described in original Claim 12. Claim 12 has been canceled. Claim 13 has been amended to depend from Claim 11. These amendments do not add new matter to the present application.

Claim 24, and page 25 have been amended to correct compound 116 to correspond to Example 111 and be named "2-(N,N',N'-trimethyl-ethylenediamino)-4-(2-pyridyloxy)-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyrimidine". Claim 24 and Compound 110 have been amended to correct "piperidyl" to be "piperidinyl" to correct a typographical error. The name of Example 105, which corresponds to Compound 110 of Claim 24, has been amended on page 137, line 21 of the specification to correct "piperidyl" to be "piperidinyl" to correct a typographical error. Claim 24 and Compound 117 have been amended to correct "pyrrolindyl" to be "pyrrolidinyl" to correct a

typographical error. The name of Example 112, which corresponds to Compound 117 of Claim 24, has been amended on page 141, line 11 of the specification to correct "pyrrolindyl" to be "pyrrolidinyl" to correct a typographical error. Additionally, Claim 24 has been amended to correct compound 46 where "pyrrolidyl should be "pyrrolidinyl"; to correct compound 52 where n -(3-methyl)butyryl should be "N -(3-methyl)butyryl"; and the period following compound 150 has been replaced with a comma. The name of Example 40, which corresponds to Compound 46 of Claim 24, has also been amended on page 100, line 21 of the specification to correct "pyrrolidyl" to be "pyrrolidinyl" to correct a typographical error. Finally, Claim 24 has been amended to delete: compound (13) 2-amino-4-(2,4-dichlorophenyl)-5-(4-chlorophenyl)pyrimidine; compound (15) 2-methylthio-4-(3,4-difluorobenzyloxy)-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyrimidine; compound (16) 2-methylthio-4-hydroxy-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-pyrimidine; and compound (19) 2-methylthio-4-hydroxy-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyrimidine.

These amendments do not add new matter to the present application and serve to avoid possible confusion caused by typographical errors.

New Claim 25 has been added directed to a method for treating substance abuse disorders wherein the abused substance is nicotine in a person dependent on nicotine comprising administering a therapeutically effective amount of a compound according to Claim 1 to the person. Support for new Claim 25 is found in the specification on page 3, lines 7-9 and page 48, lines 18-30 of the specification.

Reconsideration of the application as amended above is respectfully requested.

Claim Rejections - 35 U.S.C. § 112

The Examiner rejected Claims 2-9 and 24, presently Claims 2, 4-9 and 24, under 35 U.S.C. § 112, second paragraph, as being indefinite or failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that recitation of "and pharmaceutically acceptable salts thereof" in Claims 2-9 and 24, renders these claims indefinite as it is not clear whether these claims are compound claim or composition claim with above said limitations.

Applicants have amended Claims 2, 4-9 and 24 by replacing "and pharmaceutically acceptable salts thereof" with the proper Markush recitation in the alternate form "or a pharmaceutically acceptable salt thereof." In view of these amendments, Applicants request reconsideration and withdrawal of the rejection of claims 2-9 and 24, presently Claims 2, 4-9 and 24, under 35 U.S.C. § 112, second paragraph.

The Examiner rejected Claims 11-16, presently Claims 11 and 13-16, under 35 U.S.C. § 112, first paragraph, asserting that the specification, while being enabling for treating obesity, does not

reasonably provide enablement for treating any disease or disorder mediated by cannabinoid (CB-1) receptor. In particular, the Examiner stated:

> The instant Claims 11-16 are drawn to treating a cannabinoid receptor mediated disease by inhibiting the activity of cannabinoid receptor in general or CB-1 receptor in specific. The scope of the claims includes any or all diseases and disorders due to cannabinoid receptor inhibition activity including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 1-2 and 156-157. The instant compounds are disclosed to have cannabinoid receptor inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which appellants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cannabinoid receptor inhibitor that would be useful for all sorts of diseases and disorders, including, psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuroinflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accident, and head trauma anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia, substance abuse disorders, eating disorders, constipation and chronic intestinal pseudo-obstruction, as well as for the treatment of asthma, and cirrhosis of the liver.
> However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease, Parkinson's disease, cancers, autoimmune diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".
> The scope of the Claim 16 includes not only treating but also "preventing obesity" which is not adequately enabled solely based on the activity of the compounds as inhibitors of cannabinoid-1 receptor activity provided in the specification.. . .
> The scope of the claims involves all of the thousands of compounds of Claim 1 as well as the thousand of diseases embraced by the terms a disease or disorder and cancer.
> Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

Applicants respectfully traverse the rejection of Claims 11-16, presently Claims 11 and 13-16, under 35 U.S.C. § 112, first paragraph for not being enabled for treating diseases or disorders other than obesity. Claim 11 has been amended to incorporate the specific conditions described in original Claim 12. Claim 12 has been canceled. Claim 13 has been amended to depend from Claim 11.

As amended, Claim 11 specifies the following conditions which may be treated by administration of the compounds of the present invention: psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuroinflammatory disorders, cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders, constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, obesity, and other eating disorders associated with excessive food intake.

The treatment of asthma with CB1 inverse agonists/antagonists is supported in the literature as described in the specification on page 2, lines 6-9. The treatment of cirrhosis of the liver with the CB1 inverse agonist/antagonist compounds of the present invention is supported by the literature as

cited in the specification on page 2, lines 10-13.

Prior to the September 27, 2002 filing date of the present application, the following uses for CB-1 antagonists/inverse agonists were found in the literature: 1) Pertwee et al, Curr. Med. Chem., (1999) 6, 635-664 disclosed the potential utility of CB1 antagonists and inverse agonists as appetite suppressants, to manage acute schizophrenia, and for ameliorating cognitive/memory dysfunctions associated with disorders such as Alzheimer's disease; 2) Landsman et al, Europ. J. Pharm. 334 (1997) R1-R2 showed that CB1 inverse agonists, such as SR141716A, reduce memory deficits in aged rats and improved social recognition in adult rats; 3) Arnone et al, Psychopharm. (1997) 132:104-106 showed that CB1 antagonists, such as SR141716, reduce sucrose feeding, drinking and ethanol consumption and may have potential for the treatment of carbohydrate craving and ethanol abuse; 4) Colombo et al, Life Sciences, Vol. 63, No. 8, pp. PL 113-117 (1998) showed that CB1 antagonists, such as SR141716, reduce food intake and body weight in non-obese Wistar rats and in obese Zucker rats; 5) Rowland et al, Psychopharm. (2001) 159: 111-116 showed that CB1 antagonists, such as SR141716, suppressed food intake in both undeprived rats and food intake after deprivation; and 6) Izzo et al, Europ. J. Pharm., 384 (1999) 37-42, showed that CB1 antagonists, such as SR141716A, increased defaecation, increased faecal water content and increased upper gastrointestinal transit, which Applicants submit may make SR141716 useful to treat constipation, and chronic intestinal pseudo-obstruction. Xiang et al., Ann. Report Med Chem, (1999) 34, 199-208 teaches that delta 9-THC, a partial agonist at the CB1 receptor, causes impairment in memory and learning, affects the cardiovascular system by inducing tachycardia and hypotension, and produces peripheral effects related to bronchial constriction, immunomodulation, and inflammation. Applicants submit that based on these physiological responses by delta 9-THC, CB1 inverse agonists or antagonists may be useful to treat memory impairment, and inflammation.

Further scientific publications after the filing date of the present application confirm the use of CB1 antagonists to treat Parkinsonian symptoms, to prevent relapse to heroin abuse, to alleviate neuropathic pain and to treat psychosis. Tzavara et al, Br J Pharmacol, 2003 Feb; 138(4):544-53 disclosed the utility of CB1 antagonists, such as SR 141716A, to treat psychosis. Van der Stelt et al., The FASEB Joural, FJ Express, 19 (2005) 1140-1142 disclosed the utility of CB1 receptor antagonist rimonabant to alleviate Parkinsonian symptoms as a monotherapy. Fattore et al, Neuropharmacology, 48 (2005) 1097-1104 showed that CB1 antagonist SR 141716A attenuates reinstatement of heroin self-administration in heroin abstinent rats. Costa et al, Pain, 2005 Jul; 116 (1-2): 52-61 discloses that CB1 antagonist SR 141716 is effective in alleviating neuropathic pain.

Although the Examiner discussed the use of the term "cancer" at length, Claims 11-16, presently Claims 11 and 13-16, do not discuss the treatment of cancer.

Applicants assert that there is support for prevention of obesity as claimed Claim 16 in the specification of the present application as filed. Applicants submit that the specification at page 44,

lines 12-14 discloses present compounds may prevent obesity in a subject at risk for obesity. A subject at risk for obesity is defined on page 43, lines 9-11 as an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2, or a subject with at least one co-morbidity with a BMI of 25 kg/m2 to less than 27 kg/m^2. An obese subject is defined on page 43, lines 7-9 as having a BMI greater than or equal to 30 kg/m^2, or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2. By treating an overweight or normal weight subject, that is not yet obese based on BMI definitions, with the compounds of the present invention, it is possible to prevent the subject from gaining additional weight and becoming obese. Prevention of obesity is defined as "reducing or maintaining bodyweight of a subject at risk of obesity" on page 44, lines 12 -26 of the specification. Applicants submit that based on this support for prevention of obesity in the specification, Claim 16 should be allowed.

The Examiner suggests that one of ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed. Applicants respectfully disagree. The specification describes the compounds, how the compounds are used, and describes how and in what dosage to administer these compounds. The structures of the compounds of the present invention are given in Claims 1-9 and 24, and on pages 1-29 and 58-156 of the specification. Routes of administration for the compounds of the present invention are recited on page 34, line 1 to page 35, line 32. The dosage ranges for the compounds of the present invention are listed on page 32, line 25 to page 33, line 11. Screening assays and functional assays for CB1 inverse agonists/antagonists are given on page 156, line 16 to page 157, line 23 of the specification. Given the specification disclosures of: 1) the utility of CB1 inverse agonists/antagonists; 2) the screening assays for CB1 inverse agonists/antagonists; 3) the routes of administration of the claimed compounds; 4) the dosage ranges; and the literature support for the utility of CB1 inverse agonists/antagonists, Applicants respectfully submit that Claims 11-16, presently Claims 11 and 13-16 are enabled and should be allowed.

In view of the amendment and the remarks above, Applicants respectfully request that the rejection of claims 11-16, presently Claims 11 and 13-16, under 35 U.S.C. § 112, first paragraph be withdrawn.

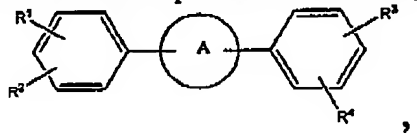
Claim Rejections - 35 U.S.C. § 102

Claims 1-8 and 17, presently Claims 1, 2, 4-8 and 17, were rejected under 35 U.S.C. § 102(e) as being anticipated by Agarwal et al., WO 2004/009560. The Examiner stated that Agarwal et al. teaches several substituted pyrimidine compounds useful as cyclooxygenase inhibitors for treating pain and other diseases, which include compounds generically claimed in the instant claims, see page 9, formula I and note that definition of A, R^1 R^2, R^3, R^4, R^5 and R^6. The Examiner further stated:

Note with a given A choice, when R^5 and R^6 are either aryl or heteroaryl, compounds taught by Agarwal et al. include instant compounds. See entire document, especially pages 13-17 for various substituted pyrimidine compounds. Particularly see page 16, species on line 9-11, 13, 14 and 18. See also examples 7 through 215, pages 33-37, wherein the starting material uracils are also claimed in the instant claims.

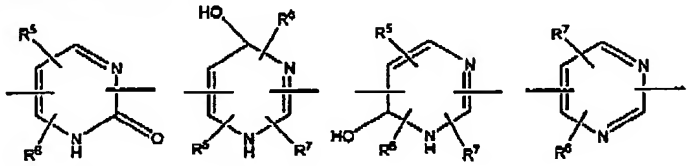
Applicants have amended Claim 1 of the present invention to delete hydrogen, S-C_{1-6} alkyl, and amino from the Markush group for R^1. Applicants respectfully submit that the Agarwal compounds do not fall within the scope of amended Claim 1 of the present invention, or within Claims 2-8 and 17, which depend from Claim 1 and incorporate the amendment to Claim 1. Applicants further submit that the compounds disclosed by Agarwal in WO 2004/009560 do not anticipate the presently amended claims.

WO 2004/009560 Agarwal teaches compounds of the following structure:



,

in which A is selected from :

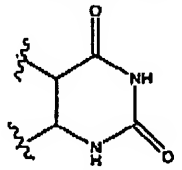


(1) (2) (3) (4)

The compounds of the present application do not allow for oxo substitution between the pyrimidine nitrogens as shown in the Agarwal compounds in which A is (1). The compounds of the present invention are pyrimidines and are fully unsaturated having 3 double bonds unlike the Agarwal compounds in which A is (2) or (3). The presently claimed invention does not allow a hydrogen or phenyl R^1 substituent between the pyrimidine nitrogens (R^1 group), and the Agarwal compounds in which A is (4) do not fall within the scope of the presently amended claims. Applicants submit that the Agarwal compounds in which A is (1), (2), (3), or (4) are not within the scope of the presently amended claims and do not anticipate the presently amended claims.

Each Agarwal species disclosed on pages 13-17 of WO 2004/009560 provides a chloro, azide, hydrazine, trifluoromethyl, methylthio, or hydroxy substituent at the 4 position of the Agarwal A ring, and some of the species provide hydrogen substitution between the Argawal A ring nitrogens. However in the compounds of the present invention, R^2 and R^4 cannot be chloro, azide, hydrazine, trifluoromethyl, methylthio, or hydroxyl, and, as amended, $R^1$is not hydrogen. Therefore, the Agarwal compounds disclosed on pages 13-17 are outside of the scope of the presently amended claims.

Agarwal Examples 7-15 on pages 33-37 of WO 2004/009560 disclose compounds in which the 4 position (corresponding to the R^2 or R^4 substituent in the present invention) is substituted with chloro and azide and the 2 position between the A ring nitrogens (corresponding to our R^1 substituent) is substituted with chloro or trifluoromethyl. However, in the compounds of the present invention, R^2 and R^4 cannot be chloro or azide, and R^1 cannot be chloro or trifluoromethyl. Finally, the uracil starting materials for Agarwal Examples 7-15 have the following core structure:



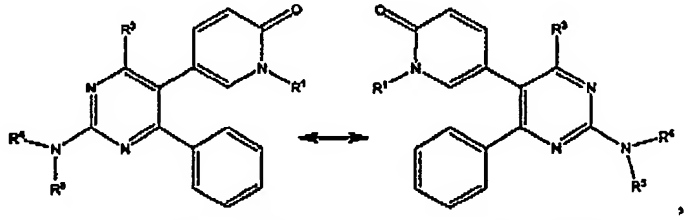
and do not fall within the genus of the present application because the compounds of the present application do not allow the R^1 substituent to be an oxo group.

Applicants submit that the Agarwal compounds do not fall within the scope of amended Claim 1 of the present invention, or within Claims 2-8 and 17, which depend from Claim 1 and incorporate the amendment to Claim 1. Applicants further submit that the compounds disclosed by Agarwal in WO 2004/009560 do not anticipate the presently amended claims.

Applicants respectfully request that the rejections of claims 1-8 and 17, presently Claims 1-2, 4-8 and 17, under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-8, 11, 12, and 17, presently Claims 1, 2, 4-8, 11 and 17, were rejected under 35 U.S.C. § 102(e) as being anticipated by Akahane et al., WO 2004/016605. The Examiner stated that Akahane et al. teaches several 2-aminopyrimidine compounds useful for treating dementia and depression, which include instant compound generically claimed in the instant claims. In particular, the Examiner pointed to page 4, formula I and the definition of R^1, R^2, R^3, R^4 and R^5. The Examiner state that with a given R^3 choice, compounds taught by Akahane et al. include instant compound.

Applicants have amended Claim 1, upon which Claims 2, 4-8, 11 and 17 directly or indirectly depend, to define R^3 as 2-pyridyl and phenyl. Akahane in WO 2004/016605 discloses the following compounds:



in which the pyrimidine ring is substituted with an oxo substituted 3-pyridine group. The compounds disclosed in Examples 1-27 on pages 38-48 and in the process steps on pages 5-12 contain either a methoxy or oxo substituted 3-pyridine substituent on the pyrimidine ring. As amended, the present invention does not provide for R^3 as 3-pyridyl, and does not allow for oxo substitution on the R^3

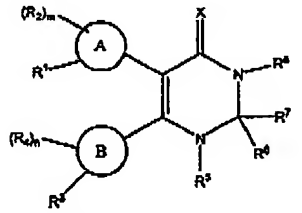
group. As amended, the compounds disclosed in Akahane do not fall within the scope of Claim 1 of the present invention, or within Claims 2, 4-8, 11, and 17, which depend from Claim 1 and incorporate the amendment to Claim 1. Applicants further submit that the compounds disclosed by Akahane do not anticipate the compounds claimed in the presently amended application.

Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-8, 11, 12, and 17, presently Claims 1, 2, 4-8, 11 and 17, under 35 U.S.C. § 102(b).

Claims 1-8 and 17, presently Claims 1, 2, 4-8, and 17, were rejected under 35 U.S.C. § 102(e) over Agarwal et al., WO 03/084935. The Examiner stated that Agarwal et al. teaches several diaryl pyrimidine compounds useful as cyclooxygenase inhibitors for treating pain and other diseases, in particular, see page 9, formula 1 and note the definition of A, B, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8. The Examiner further stated that with a given A and B choices, when R^5 and R^6 form double bond, compound taught by Agarwal et al. include instant compounds.

Applicants respectfully traverse the rejection of Claims 1-8 and 17, presently Claims 1, 2, 4-8, and 17, under 35 U.S.C. § 102(e) over Agarwal et al., WO 03/084935.

Argarwal et al. WO 03/084935 ("Agarwal 2") discloses compounds of the following structure:



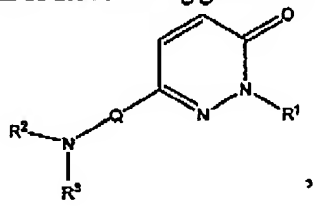
in which X is O, NR or S. In the Agarwal 2 compounds on pages 14-15 and in Examples 5-20 on pages 38-47, X is oxygen, and the carbon between the ring nitrogens is substituted with =O or =S. The R^2 and R^4 groups of compounds of the present invention do not allow for =O, =S or =NR substitution; and the R^1 group of the present invention does not include oxygen or =O. As a result, the Agarwal 2 compounds are not within the scope of the present claims. Additionally, even if R^5 and R^6 of the Agarwal 2 compounds form a double bond, the resulting Agarwal 2 compounds do not have a pyrimidine core because they lack the third double bond within the ring. Applicants submit that Claim 1 is novel and distinct from the compounds disclosed in Agarwal 2. Still further, the compounds disclosed in Claims 2-8 and 17, presently Claims 2, 4-8 and 17, incorporate the limitations of Claim 1, and are novel and distinct from the Argarwal 2 compounds. Applicants further submit that the compounds disclosed by Agarwal do not anticipate the compounds in the presently amended claims.

Applicants respectfully request that the rejections of Claims 1-8 and 17, presently Claims 1, 2, 4-8 and 17, under 35 U.S.C. § 102(b) over Argarwal 2 be withdrawn.

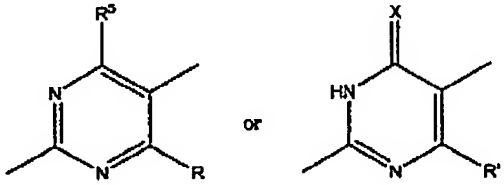
Claims 1-8, 11, 12 and 17, presently Claims 1, 2, 4-8, 11 and 17, were rejected under 35 U.S.C. § 102(e) over Tsutsumi et al. US 2005/0043315. The Examiner noted that Tsutsumi et al. teach several aminopyrimidine compounds useful for treating dementia and depression, in particular, page 1, formula 1 and the definition of Q, R^1, R^2 and R^3. The Examiner stated that with a given Q choices, compounds taught by Tsutsumi et al. include instant compound, and noted particularly page 3-7 for various process of making aminosubstituted pyrimidine compounds, and pages 30-69, example 1 through 253 for compounds made.

Applicants have amended Claim 1 of the present invention to define R^3 as 2-pyridyl or phenyl. As amended, the presently claimed compounds are novel and distinct from the compounds disclosed in Tsutsumi.

Tsutsumi teaches compounds of the following general structure:



in which Q is defined as:



The Tsutsumi compounds disclosed in formula 1 on page 1 and pages 3-7 all contain a Q core substituted with an oxo substituted pyridazine group. As amended, the R^3 substituent of Claim 1 in the present invention cannot be pyridizine. Claim 1 is novel and distinct from the compounds disclosed in Tsutsumi. Still further, dependent Claims 2-8, 11, 12 and 17, presently Claims 2, 4-8, 11 and 17, which depend, directly or indirectly from Claim 1 and incorporate the limitations of Claim 1 are also novel and distinct from Tsutsumi. Applicants further submit that the compounds disclosed by Tsutsumi in US 2005/0043315 do not anticipate the compounds in the presently amended claims.

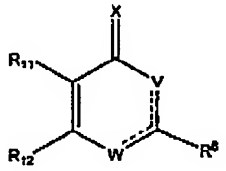
Applicants respectfully request that the rejections of Claims 1-8, 11, 12 and 17, presently Claims 1, 2, 4-8, 11, and 17, under 35 U.S.C. § 102(b) over Tsutsumi be withdrawn.

Claims 1-8, presently Claims 1, 2, and 4-8, were rejected under 35 U.S.C. § 102(b) as being anticipated by Spohr et al., US 6,096,753. The Examiner stated that Spohr et al. teaches several substituted pyrimidine compounds, for treating pain and other diseases, which include the intermediates of the compounds claimed in the instant claims, and noted column 2, formula 1 and the

definition of various variable groups. The Examiner further stated that when the core is pyrimidine of formula shown on column 5, line 5, R_{11} and R_{12} is aryl or heteroaryl, compounds taught by Spohr et al. include instant compounds.

Applicants respectfully traverse the rejection of Claims 1-8, presently Claims 1, 2, and 4-8, under 35 U.S.C. § 102(b) over Spohr et al.

Spohr et al. discloses pyrimidinone and pyridinone compounds of the following general structure:

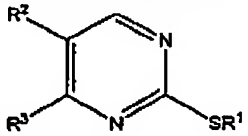


wherein X is O, NR^5 or S. The Spohr compounds cited by the Examiner (which are the compounds in column 2 formula 1, with the pyrimidine core of the formula shown on column 5, in the Table spanning columns 21 through 43 and in Examples 1-57, columns 61-122) are pyrimidinone compounds in which the core pyrimidine ring is substituted with a carbonyl group (=O). The compounds of the present invention do not provide for substitution of the pyrimidine ring with oxo or a carbonyl group. The R^2 and R^4 substituents of pyrimidine compounds of the present invention do not allow for =O substitution. Additionally, the Spohr et al. compounds do not have a pyrimidine core because they lack the third double bond in the ring. Applicants submit that the compounds of the invention, as claimed in Claims 1, 2, and 4-8, are novel and distinct from those disclosed by Spohr et al. in US 6,096,753 . Applicants submit that the compounds disclosed by Spohr do not anticipate the compounds claimed in the presently amended application.

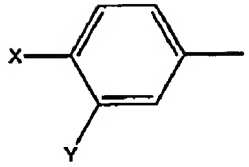
Applicants respectfully request that the rejections of Claims 1-8, presently Claims 1, 2, and 4-8, under 35 U.S.C. § 102(b) over Spohr et al. be withdrawn.

Claims 1-8, presently Claims 1, 2, and 4-8, were rejected under 35 U.S.C. § 102(b) over anticipated by Cherkofsky US 4,438,117 which the Examiner stated teaches several 2-substituted thio-4,5-diarylpyrimidine compounds for treating arthritis, including column 1, formula shown in line 45. The Examiner stated, "Especially note when R_1 and R_1 is aryl or pyridyl, compounds taught by Cherkofsky include instant compounds."

In US 4,438,117, Cherkofsky discloses compounds with the following structure:



in which R^2 and R^3 are independently 3-pyridyl or



The Cherkofsky compounds disclosed in examples 1-15 all contain the $-SR^1$ substituent wherein R^1 is defined as mono or polyfluoro-C_1-C_2alkyl or C_1-C_2alkyl.

Applicants have amended R^1 in Claim 1 to delete $-SR^b$ from the Markush group, and to specify that R3 and R4 are selected from substituted phenyl and substituted 2-pyridyl. Applicants have also amended Claim 4 to delete $-SC_{1-6}$alkyl in element (24), and Claim 24 to delete compounds 15, 16 and 19 from the Markush group of claimed compounds. As amended, the compounds of Claims 1 and dependent Claims 2, and 4-8 are not directed to compounds with an alkylthio or a fluoridated alkylthio substituent at the 2-position of the pyrimidine. Still further, the compounds of the present invention do not include 3-pyridyl substituents at the 4 or 5 position. Cherkofsky does not teach or suggest the presently claimed compounds of Claim 1 nor of Claims 2, and 4-8 which depend from Claim 1 and incorporate the limitations therein. Applicants further submit Cherkofsky does not anticipate the presently claimed invention.

Applicants respectfully request that the rejections of claims 1-8 under 35 U.S.C. § 102(b) over Cherkofsky be withdrawn.

Claims 1-3 and 7, presently Claims 1, 2 and 7, were rejected under 35 U.S.C. § 102(b) as being anticipated by Olivera et al., Tetrahedron 58(15):3021-3037, 2002, which the Examiner stated teaches several 2,6-unsubstituted-4,5-diarylpyrimidine compounds.

All of the compounds disclosed in Olivera, including the compounds on pages 3022-3024, are unsubstituted on the carbon between the N and Y groups (which corresponds to being unsubstituted on the carbon between the pyrimidine nitrogens). Applicants have amended Claim 1 by deleting hydrogen from the Markush group for R^1, and have canceled Claim 3. Applicants submit that the presently claimed invention in Claim 1 and dependent Claims 2 and 7 is not taught or disclosed by Olivera. Applicants further submit that the compounds disclosed by Olivera do not anticipate the compounds in the presently amended claims.

Applicants respectfully request that the rejections of Claims 1-3 and 7 under 35 U.S.C. § 102(b) over Olivera be withdrawn.

Claims 1-3 and 7, presently Claims 1, 2 and 7, were rejected under 35 U.S.C. § 102(b) over Huang et al., Gaodeng Xuexiao Huaxue Xuebao 16(11): 1740-1743, 1995, CA 124: 317095, 1996. The Examiner stated that Huang teaches several pyrimidine compounds, which include compounds claimed in the instant claims.

The Huang CAPLUS Abstract CA 124: 317095, discloses compounds which would correspond to the compounds of the present compounds in which R^1 is $-NH_2$, =S or $-CF_3$. However, in the compounds of the present invention, R^1 is does not include =S or CF_3. Applicants have amended Claim 1 to delete $-NH_2$ from the definition of R^1 by proviso. Applicants have also amended Claim 5 to delete NR^aR^b where R^a is hydrogen, and Claim 8 to delete R^1 is amino in element (10). Still further, Applicants have amended Claim 24 to delete compound 13 from the Markush group of compounds. Thus, as amended, R^1 is not $-NH_2$, =S or $-CF_3$. The Huang reference does not teach or disclose the subject matter claimed by Claims 1, and dependent Claims 2 and 7. Applicants further submit that the compounds disclosed by Huang do not anticipate the compounds claimed in the presently amended application. Applicants respectfully request that the rejections of Claims 1-3 and 7, presently Claims 1, 2and 7, under 35 U.S.C. § 102(b) over Huang be withdrawn.

Claims 1-8, presently Claims 1, 2, and 4-8, were rejected under 35 U.S.C. § 102(b) over Fischer et. al., DD 294255, CA 116: 128952, 1992, which the Examiner stated teaches several pyrimidine compounds.

Applicants respectfully traverse the rejection of Claims 1, 2, and 4-8 under 35 U.S.C. § 102(b) over Fischer. The compounds disclosed by Fischer contain a tetrazole ring substituted with a phenyl group. However, the claimed compounds of the present invention do not allow phenyl substitution on the R^3 heteroaryl substituent (R^2 cannot be phenyl). Further, Claim 1 of the present application has been amended to define R^3 as 2-pyridyl and phenyl, as a result R^3 cannot be a tetrazole. Applicants submit that Fischer does not teach or disclose the invention compounds claimed in Claim 1 or dependent Claims 2, and 4-8, which depend from Claim 1. Applicants further submit that the compounds disclosed by Fischer do not anticipate the compounds claimed in the present application, and respectfully request that the rejections of Claims 1-8, presently Claims 1, 2, and 4-8, under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-8, presently Claims 1, 2 and 4-8, were rejected under 35 U.S.C. § 102(b) as being anticipated by Khilya et al., Chemistry of Natural Compounds (Translation of Khimya Prirodnykh Soedinenii) 37(4): 307-310, 2001, CA 137: 78805, 2002 because the Examiner noted that Khilya teaches several pyrimidine compounds.

The Applicants submit that each Khilya pyrimidine compound contains a hydroxy substituted 1,4-benzodioxan ring at the R^2, R^3 or R^4 position of the present invention. The R^2 substituent of the present invention cannot be aryl or 1,4-benzodioxan. Still further, Applicants have amended Claim 1 of the present application to define R^3 and R^4 as 2-pyridyl and phenyl, as a result R^3 and R^4 cannot be 1,4 benzodioxan. Therefore, as amended, the present invention does not encompass compounds wherein any of R^2, R^3 or R^4 is hydroxy-substituted 1,4-benzodioxan. Applicants submit that the

Khilya reference does not teach or disclose the invention as claimed in amended Claim 1 or Claims 2, and 4-8, which depend from Claim 1 and incorporate the limitations of Claim 1. Applicants further submit that the compounds disclosed by Khilya do not anticipate the compounds claimed in the presently amended application.

Applicants respectfully request that the rejections of Claims 1-8, presently Claims 1, 2, and 4-8, under 35 U.S.C. § 102(b) over Khilya be withdrawn.

Claims 1-8, presently Claims 1, 2, and 4-8, were rejected under 35 U.S.C. § 102(b) as being anticipated by Khilya et al., Khimya Geterotsiklicheskikh Soedinenii, 11: 1542-1550, 1985, CA 105: 208819, 1986. ("Khilya 2"), which the Examiner stated teaches several pyrimidine compounds.

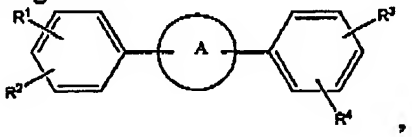
The pyrimidine compounds disclosed in Khilya 2 each contain either a hydroxy or acetoxy substituted phenyl substituent on the pyrimidine ring. Although the R^3 and R^4 groups of the present invention can be phenyl rings, the R^3 and R^4 phenyl rings cannot be substituted with a hydroxyl (-OH) or an acetoxy (-OAc) group in the compounds of the present invention (R^8 cannot be –OH or –OAc). Applicants respectfully submit that the Khilya 2 reference neither teaches nor discloses the claimed invention of Claim 1, nor the claimed subject matter of dependent Claims 2, and 4-8, which incorporate the limitations of Claim 1. Applicants further submit that Khilya 2 does not anticipate the compounds claimed in the present application.

Applicants respectfully request that the rejection of Claims 1-8, presently Claims 1, 2 and 4-8, under 35 U.S.C. § 102(b) over Khilya 2 be withdrawn.

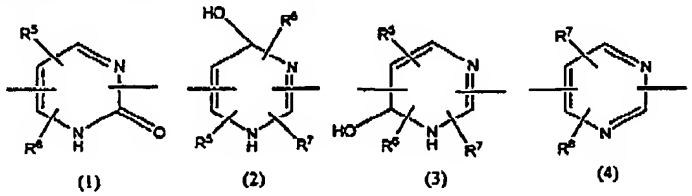
Claim Rejections - 35 U.S.C. § 103

Claims 1-9, 17 and 24, presently Claims 1,2, 4-9, 17 and 24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Agarwal et al., WO 2004/009560.

Applicants respectfully traverse the Examiner's rejection of Claims 1-9, 17 and 24 as obvious over Agarwal et al. The compounds of the present invention and their use are not *prima facie* obvious. Applicants respectfully submit that Agarwal et al. does not teach or suggest the compounds claimed in the presently amended application. Applicants submit that in WO 2004/009560 Agarwal teaches compounds of the following structure:

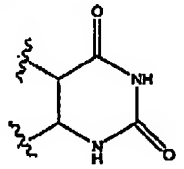


in which A is selected from:



The compounds of the present application do not allow for oxo substitution between the pyrimidine nitrogens as shown in the Agarwal compounds in which A is (1). The compounds of the present invention are pyrimidines and are fully unsaturated having 3 double bonds in the ring unlike the Agarwal compounds in which A is (2) or (3). Applicants have amended Claim 1 of the present invention to delete R^1 is hydrogen and further submit that in the compounds of the present invention R^1 cannot be phenyl. Based on this amendment, the compounds of the present invention do not allow a hydrogen or phenyl substituent between the pyrimidine nitrogens, and the Agarwal compounds in which A is (4) do not fall within the scope of the presently amended claims. Applicants submit that the Agarwal compounds in which A is (1), (2), (3), or (4) are not within the scope of the presently amended claims.

Each Agarwal species disclosed on pages 13-17 of WO 2004/009560 allows a chloro, azide, hydrazine, trifluoromethyl, methylthio, or hydroxy substituent at the 4 position of the A ring, and some of the species allow hydrogen substitution between the A ring nitrogens. However in the compounds of the present invention, R^2 and R^4 cannot be chloro, azide, hydrazine, trifluoromethyl, methylthio, or hydroxyl, and R^1 has been amended to delete hydrogen. Therefore the Agarwal compounds disclosed on pages 13-17 are outside of the scope of the presently amended claims. Agarwal examples 7-15 on pages 33-37 of WO 2004/009560 disclose compounds in which the 4 position (corresponding to our R^2 or R^4 substituent) is substituted with chloro and azide and the 2 position between the A ring nitrogens (corresponding to our R^1 substituent) is substituted with chloro or trifluoromethyl. However, in the compounds of the present invention, R^2 and R^4 cannot be chloro or azide, and R1 cannot be chloro or trifluoromethyl. Finally, the uracil starting materials for Agarwal Examples 7-15 have the following core structure:



and do not fall within the genus of the present application because the compounds of the present application do not allow the R^1 substituent to be oxo substituent.

Applicants submit that there is no teaching, suggestion or motivation in Agarwal to one of ordinary skill in the art to modify Agarwal compounds stated to be useful for the treatment of inflammation and immunological diseases mediated by cytokines such as TNF-alpha, IL-1, IL-6, IL-1beta, IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3, to obtain the presently claimed compounds of Claims 1, 2, 4-9, 17 and 25, useful as antagonists/inverse agonists of the cannabinoid 1 receptor. Based on the Agarwal reference it would not have been obvious to one of ordinary skill in

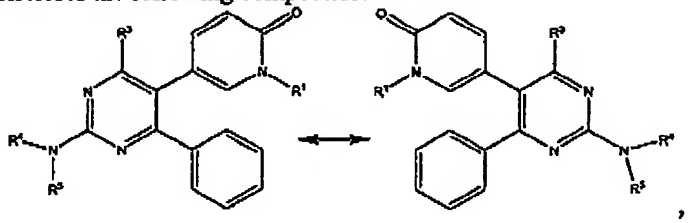
the art to make the presently claimed compounds or to use the presently claimed compounds to treat diseases mediated by the CB-1 receptor.

In view of this amendment and the remarks above, Applicants respectfully request that the rejections of Claims 1-9, 17 and 24, presently Claims 1, 2, 4-9, 17 and 24, under 35 U.S.C. § 103(a) over Agarwal be withdrawn.

Claims 1-9, 11, 12, 17 and 24, presently Claims 1, 2, 4-9, 11, 17 and 24, were rejected under 35 U.S.C. § 103(a) as being unpatentable over Akahane et al., WO 2004/016605. The Examiner stated that Akahane et al. differs from the instant claims in exemplifying only some of the compounds embraced in the genus of compound of formula 1 shown in page 4; however, Akahane et al. teaches equivalency of those compounds taught in pages 38-48, examples 1-27 with those generically recited for formula 1 in page 4, and thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Akahane et al. and expect resulting compounds to possess the uses taught by the art.

Applicants respectfully traverse the Examiner's rejection of Claims 1-9, 11, 12, 17 and 24, presently Claims 1,2, 4-9, 11 and 17, as obvious over Akahane, because the compounds of the present invention and their use are not *prima facie* obvious. Applicants submit that Akahane does not teach, suggest, or motivate one of ordinary skill in the art to arrive at the compounds in the presently amended claims.

Akahane discloses the following compounds:



in which the pyrimidine ring is substituted with an oxo substituted 3-pyridine group. The compounds disclosed in Examples 1-27 on pages 38-48 and in the process steps on pages 5-12 contain either a methoxy or oxo substituted 3-pyridine substituent on the pyrimidine ring. Applicants have amended Claim 1 to define R^3 as 2-pyridyl and phenyl. Based on this amendment, the current claims of the present invention do not allow R^3 to be 3-pyridyl, and do not allow for oxo substitution on the R^3 group.

Applicants submit that the compounds disclosed in Akahane and the compounds of the presently amended application are not structurally or functionally equivalent. The Akahane reference does not provide motivation to modify the compounds therein to obtain the compounds of the amended claims which are useful to treat diseases mediated by the CB-1 receptor. The compounds disclosed in Akahane et al. are adenosine antagonists useful for treating dementia and depression. Akahane does not teach or suggest that the compounds disclosed in Akahane are useful as CB-1

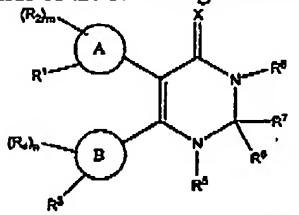
antagonists or inverse agonists, or that they are useful to treat diseases mediated by the CB-1 receptor. Based on the Akahane reference it would not have been obvious to one of ordinary skill in the art to make the presently claimed compounds or to use the presently claimed compounds to treat diseases mediated by the CB-1 receptor.

In view of these amendments and the remarks above, Applicants respectfully request that the rejections of Claims 1-9, 11, 12, 17 and 24, presently Claims 1, 2, 4-9, 11, 17 and 24, under 35 U.S.C. § 103(a) over Akahane be withdrawn.

Claims 1-9, 17 and 24, presently Claims 1, 2, 4-9, 17 and 24, were rejected under 35 U.S.C. § 103(a) as being unpatentable over Agarwal et al., WO 03/084935, ("Agarwal 2"). The Examiner stated that Agarwal 2 teaches equivalency of those compounds taught on pages 38-47, examples 5-20, with those generically recited in page 9-10, and thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Agarwal 2 and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Applicants respectfully traverse the Examiner's rejection of Claims 1-9, 17 and 24, presently Claims 1, 2, 4-9, 17 and 24, as obvious over Agarwal 2, because the compounds of the present invention and their use are not *prima facie* obvious. Applicants submit that Agarwal 2 does not teach, suggest, or motivate one of ordinary skill in the art to obtain the compounds claimed in the presently amended application.

Agarwal 2 discloses compounds of the following structure:



in which X is O, NR or S. In the Agarwal 2 compounds on pages 14-15 and in Examples 5-20, X is oxygen, and the carbon between the ring nitrogens is substituted with =O or =S. The R^2 and R^4 groups of compounds of the present invention do not allow for =O, =S or =NR substitution; and the R^1 group of the present invention does not include oxygen or =O. As a result, the Agarwal 2 compounds are not within the scope of the present claims. Additionally, even if R^5 and R^6 of the Agarwal 2 compounds form a double bond, the resulting Agarwal compounds do not have a pyrimidine core because they lack a third double bond in the ring.

Applicants submit that the compounds in Agarwal 2 and the compounds of the presently amended application are not structurally or functionally equivalent. The Agarwal 2 reference does not teach or suggest the compounds of the amended claims or their use to treat diseases mediated by the

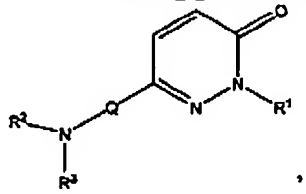
CB-1 receptor. The compounds disclosed in Agarwal 2 are useful for the treatment of inflammation and immunological diseases mediated by cytokines such as TNF-alpha, IL-1, IL-6, IL-1beta, IL-8 and cyclooxygenase such as COX-1, COX-2 and COX-3. Agarwal does not teach or suggest that the compounds disclosed in Agarwal 2 are useful as CB-1 antagonists or inverse agonists, or that they are useful to treat diseases mediated by the CB-1 receptor. Agarwal 2 does not provide any suggestion or motivation to modify the compounds disclosed therein to arrive at the presently claimed compounds. Based on the Agarwal 2 reference it would not have been obvious to one of ordinary skill in the art to make the presently claimed compounds or to use the presently claimed compounds to treat diseases mediated by the CB-1 receptor.

In view of these amendments and the remarks above, Applicants respectfully request that the rejections of Claims 1-9, 17 and 24, presently Claims 1, 2, 4-9, 17 and 24, under 35 U.S.C. § 103(a) over Agarwal 2 be withdrawn.

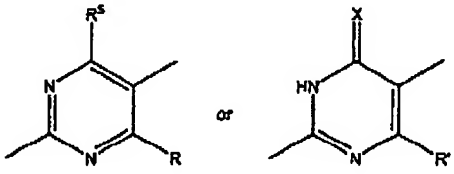
Claims 1-9, 11, 12, 17 and 24, presently Claims 1, 2, 4-9, 11, 17, and 24, were rejected under 35 U.S.C. 103(a) as being unpatentable over Tsutsumi et al. US 2005/0043315. The Examiner stated that Tsutsumi et al. differs from the instant claims in exemplifying only some of the compounds embraced in the genus of compound of formula 1 shown in page 1; however, Tsutsumi et al. teaches equivalency of those compounds taught in page 30-69, examples 1-253, with those generically recited for formula 1in page 1, and thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Tsutsumi et al. and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Applicants respectfully traverse the Examiner's rejection of Claims 1-9, 11, 12, 17 and 24, presently Claims 1, 2, 4-9, 11, 17, and 24, because the compounds of the present invention and their use are not *prima facie* obvious. Applicants submit that Tsutsumi does not teach or suggest the compounds claimed in the presently amended application.

Tsutsumi teaches compounds of the following general structure:



in which Q is defined as:



Applicants submit that the Tsutsumi compounds disclosed in formula 1 on page 1 and pages 3-7 all contain a Q core substituted with an oxo substituted pyridazine group. Applicants have amended Claim 1 of the present invention to define R^3 as 2-pyridyl or phenyl. Based on this amendment, the R^3 substituent cannot be pyridizine in the presently claimed compounds. As a result, the compounds disclosed in Tsutsumi do not fall within the scope of amended Claim 1 of the present invention.

Applicants submit that the compounds disclosed in Tsutsami and the compounds of the presently amended application are not structurally or functionally equivalent. The Tsutsami reference does not teach or suggest the compounds of the amended claims or their use to treat diseases mediated by the CB-1 receptor. The compounds disclosed in Tsutsami are adenosine antagonists useful for the treatment of dementia and depression. Tsutsami does not teach or suggest that the compounds disclosed in Tsutsami are useful as CB-1 antagonists or inverse agonists, or that they are useful to treat diseases mediated by the CB-1 receptor. Based on the Tsutsami reference it would not have been obvious to one of ordinary skill in the art to make the presently claimed compounds or to use the presently claimed compounds to treat diseases mediated by the CB-1 receptor.

Additionally as discussed above, Akahane does not teach or suggest the compounds of the present invention or their utility. Tsutsumi and Akahane, alone or in combination, do not teach or suggest the compounds of the present invention or their utility. Still further, neither Tsutsumi and Akahane, alone or in combination, provides the suggestion or motivation to modify the compounds therein to arrive at the presently claimed compounds.

In view of this amendment and the remarks above, Applicants respectfully request that the rejections of Claims 1-9, 11, 12, 17 and 24, presently Claims 1, 2, 4-9, 11, 17, and 24, under 35 U.S.C. § 103(a) be withdrawn.

Applicants respectfully contend that the application is allowable, and a favorable response from the Examiner is earnestly solicited.

Respectfully submitted,

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